Pearson BTEC Level 3 Nationals Extended Diploma

Supervised period: 6 hours

Paper reference **31629H**

Applied Science

UNIT 7: Contemporary Issues in Science

Part A

You do not need any other materials.

Instructions

- **Part A** contains material for the completion of the preparatory work for the set task.
- **Part A** is given to learners during the supervised window before **Part B** is scheduled. Learners are advised to spend no more than 6 hours on **Part A**.
- **Part A** must be given to learners on the specified date so that learners can prepare in the way specified.
- **Part A** is specific to each series and this material must only be issued to learners who have been entered to undertake the task in the relevant series.
- **Part B** materials must be issued to learners on the date specified by Pearson.

Turn over ▶

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Instructions to Teachers/Tutors

This paper must be read in conjunction with the unit information in the specification and the *BTEC Nationals Instructions for Conducting External Assessments* (ICEA) document. See the Pearson website for details.

This set task has a preparatory period. **Part A** sets out how learners should prepare for the completion of the **Part B** task under supervised conditions.

Part A is given to learners during the specified window before **Part B** is scheduled. Learners are advised to spend no more than six hours on **Part A**.

Learners should undertake independent research on the case study given in this **Part A** booklet.

Centres must issue this booklet at the appropriate time and advise learners of the timetabled sessions during which they can prepare. It is expected that scheduled lessons or other timetabled slots will be used for the preparation.

Learners should familiarise themselves with the specific concepts and terminology used in the articles.

Learners may prepare summary notes on the articles. Learners may take up to four sides of A4 notes, which may be handwritten or word processed, into the supervised assessment (**Part B** booklet).

These notes should only include information about scientific terminology, quantities and concepts used in the articles and a summary of the scientific issue discussed. This will enable learners to interpret, analyse and evaluate the articles in **Part B**. Other content is not permitted.

Part B must be completed under supervision in a single session of 2 hours and 30 minutes timetabled by Pearson.

The supervised assessment should be completed in the **Part B** task and answer booklet.

Teachers/tutors should note that:

- learners should not be given any direct guidance or prepared materials
- learners should not be given any support in writing or editing notes
- all work must be completed independently by the learner
- learner notes must be retained securely by the centre after **Part B** and may be requested by Pearson if there is suspected malpractice.

Refer carefully to the instructions in this taskbook and the BTEC Nationals *Instructions for Conducting External Assessments* (ICEA) document to ensure that the preparatory period is conducted correctly and that learners have the opportunity to carry out the required activities independently.

Instructions for Learners

Read the set task information carefully.

This is **Part A** of the set task and gives information you need to use to prepare for **Part B** of the set task.

In **Part B** you will be asked to carry out specific activities using the information in this **Part A** booklet and your preparatory notes.

In your preparation for **Part B,** using this **Part A** booklet, you may prepare short notes to refer to when completing the set task. Your notes may be up to four sides of A4 and may be handwritten or word processed. Your notes should only include information about scientific terminology, quantities and concepts used in the articles and a summary of the scientific issue discussed. This will enable you to interpret, analyse and evaluate the articles in **Part B**. Other content is not permitted.

You will complete **Part B** under supervised conditions.

You must work independently throughout the supervised assessment and must not share your work with other learners.

Your teacher/tutor may give guidance on when you can complete the preparation.

Your teacher/tutor cannot give you feedback during the preparation period.

You must not take your preparatory notes out of the classroom at any time and you must hand them in to your teacher/tutor on completion.

Your notes will be made available to you at the beginning of the supervised assessment.

Set Task Brief

You are provided with the following adapted articles:

Article 1: How stem cell research could help repair heart attack damage
https://www.bhf.org.uk/informationsupport/heart-matters-magazine/research/stem-cell-research

Article 2: Why stem cells could be the medical innovation of the century
https://www.weforum.org/agenda/2020/01/how-will-stem-cells-impact-the-future-of-medicine/

Article 3: Current state of stem cell-based therapies: an overview
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7367472/

Your notes should only include information about scientific terminology, quantities and concepts used in the articles and a summary of the scientific issue discussed.

You should spend up to a maximum of six hours to complete your preparatory notes. You may take up to four sides of A4 notes into the supervised assessment.

Part A Set Task Information

Article 1

How stem cell research could help repair heart attack damage

This is an edited version of an article published on the British Heart Foundation website on May 2021.

Professor Ian Wilmut stands beside Dolly the sheep, the world's first cloned animal.
(Source: © PA Images/Alamy Stock Photo)

Stem cell research could reveal new ways to help us mend broken hearts, as Sarah Kidner discovers.

Chances are you've heard of stem cells. Even if you haven't, you'll know of Dolly the cloned sheep – the original 'poster girl' of this sensational field of scientific research.

Twenty-five years ago, Dolly's creation saw scientists accused of 'playing God', but while stem cell research does raise ethical questions, it may also hold the answer to mending hearts damaged by a heart attack and has many other potential uses.

Two professors working in the newest areas of stem cell research tell us how their work could affect people's lives in the future.

"It's an amazing breakthrough." says Chris Denning, Professor of Stem Cell Biology at the University of Nottingham. "Ten years ago, we couldn't have conceived of these studies, but what was once impossible is now possible."

He's referring to induced pluripotent stem (iPS) cells. Their development won Shinya Yamanaka and John Gurdon the Nobel Prize for Physiology or Medicine in 2012. But what are iPS cells, and why is this type of research so important?

iPS cells explained

Until recently, to do stem cell research scientists needed to obtain human embryonic stem cells from spare IVF (*in vitro* fertilisation) embryos with the permission of the donors. These embryonic cells could be stimulated into becoming any type of human body cell.

Today, you can simply take a skin biopsy or a blood sample from a patient to obtain cells. By adding four factors to switch on four genes, these cells are genetically reprogrammed to become stem cells.

"The four factors are called the Yamanaka factors, after Shinya Yamanaka", explains Professor Denning. The beauty of the iPS cell technique is that it is so simple.

"Everybody thought Yamanaka was crazy when he presented iPS cells at a big international conference. Within a year several labs had repeated the technique. Yamanaka was a superstar; the Japanese Government invested £65.1 million in him. Just six years later, he won the Nobel Prize."

Patient in a dish

By adding specific growth factors, you can turn iPS cells into beating heart cells in a dish. This means it's possible to study people with heart conditions without conducting invasive procedures.

"Imagine you have an inherited heart condition," says Professor Denning. "I say: 'I would like to investigate it using some of your heart cells, so I need to crack your chest open and cut out a little piece of your heart. But because the cells only last a few weeks in the lab, can I come back the next week and do the same again?' It's not going to happen."

"Now, I can take a skin biopsy, do the genetic reprogramming that turn it into stem cells and keep growing them. We're still working with the same population of cells we reprogrammed in 2008 and all we took was a skin biopsy the size of a matchstick head."

Professor Denning is able to use these iPS cells to research inherited conditions that lead to sudden death. "When patients with this condition get stressed or experience strange stimuli, they can start to experience terrible arrhythmias (irregular heartbeats) that could lead to cardiac arrest," he explains.

We are reaping the harvest of several decades of painstaking research

BHF Professor Michael Schneider

"What we're able to do in a lab is mimic the person's condition in a culture dish. This is because the cells retain the genetic abnormalities present in those who donated the skin biopsy."

New drug therapies to regenerate dead cells?

'Patients in a dish' could also help create new drugs. "If you're a person with a condition and someone says they want to test 1,000 different drugs in you, you would say 'I think not' – some of them might be harmful," says Professor Denning. "But if you can replicate these things, you can ask if those drugs work when tested in a dish."

He says what makes this recent work worthwhile is seeing the impact it might have on people's lives. "Once in a while, you have a little bit of a breakthrough, but I have to say that the thing that made me happiest was when we published our 2011 paper. Our clinical colleagues forwarded it on to a patient's family and the father replied to thank us for the work we're doing in this area. That is why we're doing it."

When someone suffers a heart attack, cells in the heart are starved of oxygen and die. This can lead to the chronic and life-limiting condition heart failure, for which there's currently no cure.

We don't know how to mend or regenerate dead cells, but stem cell research could unlock new ways of doing precisely that.

BHF Professor Michael Schneider and his team at Imperial College London are leading research to explore how we can kick-start heart cells to regenerate or repair heart muscle following a heart attack.

Their focus is on the limited number of stem cells, which already exist within the heart muscle, and to "learn how they might contribute to heart repair in the case of injury," says Professor Schneider.

Specifically, the team aims to learn how the heart's own stem cells become more effective at creating new heart muscle following a heart attack. "Our main emphasis is on finding highly cloneable cells with the ability to become all the needed cell types in the heart," says Professor Schneider.

"It's too early to say how this might work, but it may be that doctors deliver drug-like molecules or hormones into the body to activate stem cells in the heart to become new cardiac muscle to treat heart attacks."

Understanding of these techniques is continually growing. "There has never been a better time to support the BHF than now," says Professor Schneider. "We are getting the benefit of many years of previous research. The advances and their progression into clinical treatments for patients have never happened at a faster rate."

Using stem cells in research

The BHF supports essential research using stem cells because we believe they have the potential to cure conditions that are incurable today.

We fund research that uses stem cells from human or animal embryos and adult tissues, because we believe that both approaches are important.

Many of the advances in stem cell research have only been possible through the knowledge and insight gained using embryonic stem cells. We recognise that this is an area some people have concerns about.

Embryonic stem cells (ESCs)

Embryonic stem cells used in research are donated by couples who have undergone *in vitro* fertilisation (IVF) treatment. They choose to donate spare embryos that would otherwise be destroyed, so that stem cells can be extracted for use in research. Only embryos at a very early stage of development (up to 14 days) can be used.

We'll only fund research using embryonic stem cells where:

- the application has been through a thorough scientific review panel, to which researchers must show that this project could not be carried out in another way
- there is a licence from the Human Fertilisation and Embryology Authority (HFEA)
- there is approval from an independent research ethics committee.

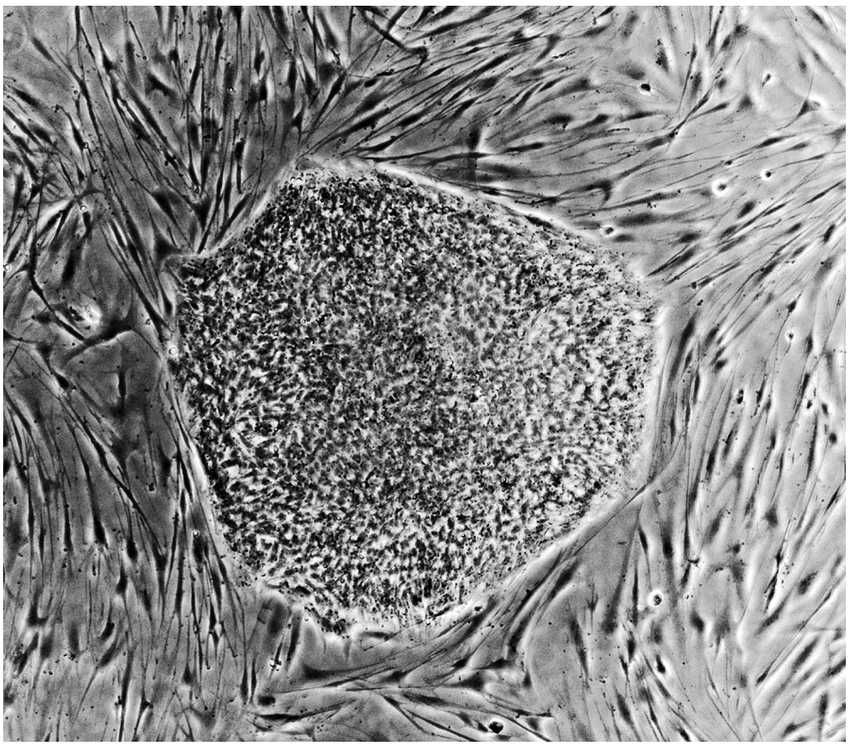
More work to be done

Heart and circulatory disease kills one in four people in the UK, but stem cell research holds real promise to help us save lives in the future.

Article 2

Why stem cells could be the medical innovation of the century

This is an edited version of an article published by the World Economic Forum in January 2020. The article was written by Mike Moradi.



A colony of embryonic stem cells
(Source: © Science Source/SCIENCE PHOTO LIBRARY)

- At the moment, the demand for stem cell therapies is growing extremely quickly and will rapidly expand when a breakthrough treatment for non-communicable disease or a lifestyle factor occurs.
- Funding is flowing into the sector from investors and large companies.
- With greater resources and an increasingly experienced talent pool, scientists and doctors may be able to develop stem cell science to cure the world's most challenging diseases.

Right now, your body's stem cells are working hard replacing your skin every two weeks, creating new red and white blood cells and completing thousands of other tasks essential to life. They are your own individual way of keeping young.

Scientists generally agree that a stem cell should be able to do both of the following:

- Self-renew: divide into another stem cell, which means making an identical copy of itself; and
- Differentiate: change into a variety of other cell types.

One theory of ageing suggests that between the ages of 30 and 50, our stem cells reach a turning point and start to decline in number and function. This results in the typical features associated with ageing.

A brief history of stem cells

There does not seem to be a single discoverer of stem cells. Accounts date back to the 1800s and even further, but the first successful medical procedure was a bone marrow transfusion[(i)] in 1939.
[(i)]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4222417/

Advances in immunology led to donor matching, initially via siblings and close relatives. Unrelated donor matching grew rapidly in the 1970s, alongside donor registries.

In the 1980s, scientists identified embryonic stem cells in mice, leading to the 1997 cloning of Dolly the sheep. This created immense interest for human and medical applications and a negative response in the US as government research and development (R&D) funding was essentially stopped in 2001.

In 2012, a Nobel Prize[(ii)] was awarded for the earlier discovery of induced pluripotent stem cells (iPS). Essentially, scientists are able to make mature cells act like stem cells again.
[(ii)]https://www.nobelprize.org/prizes/medicine/2012/press-release/

In the 10 years between 2010 and 2019, the first lot of stem cell start-up companies emerged, alongside R&D programmes at many large pharmaceutical companies, leading to innovation and the first human clinical trials for iPS and other related therapies.

Regenerative medicine in 2019

Regenerative medicine is an area of medicine that develops ways to regrow, replace or repair damaged or diseased cells, tissues or organs.

There is substantial investment in regenerative medicine across the world. According to data published in 2019, there were 959 regenerative medicine companies worldwide sponsoring 1,052 active clinical trials; 525 of these companies are in North America, 233 in Europe and Israel, and 166 in Asia. In total, $7.4 billion has been invested in regenerative medicine companies in 2019, $5.6 billion of which has been dedicated to gene and gene-modified cell therapy, $3.3 billion in cell therapy, and $114 million in tissue engineering.

Curative therapies are starting to be sold and the results are astonishing: 60% of Acute Lymphoblastic Leukaemia patients taking Novartis' Kymriah showed a complete response (no traces of cancer) and were declared in full remission. Meanwhile, 75% of patients with β-Thalassaemia treated with bluebird bio's Zynteglo achieved independence from transfusions. 93% of spinal muscular atrophy (wasting away) patients treated with Novartis' Zolgensma were alive without permanent ventilation 24 months after treatment. We should expect more medical breakthroughs in the coming years.

What is next?

New science, new start-ups: several companies in the sector have gone from being private companies to being publicly funded. This leads to the recycling of talent and capital into new companies. Because the science and commercial systems have also advanced, the new companies are pursuing bigger challenges and driving innovation with even greater resources.

Patients are eager: the demand for stem cell therapies is growing each year, though it will rapidly expand when a breakthrough occurs toward the treatment of a non-communicable disease (such as cancer, diabetes, heart disease) or a lifestyle factor (for example, growing hair in the correct places, expanding cognitive abilities or increasing healthy lifespan).

New R&D models: funding is flowing into the sector from large companies, funds from investors, and institutions such as the California Institute for Regenerative Medicine (CIRM) and New York State Stem Cell Science programme (NYSTEM). Some of the leading university R&D organisations include the Center for the Commercialization of Regenerative Medicine[iii] in Toronto, the Stanford Institute for Stem Cell Biology and Regenerative Medicine[iv], the Oxford Stem Cell Institute, and most notably, the Harvard Stem Cell Institute (HSCI)[v].

[iii]https://www.ccrm.ca/
[iv]https://med.stanford.edu/stemcell.html
[v]https://hsci.harvard.edu/startups

Where can I get some stem cells?

Though patients' needs are immediate, those seeking treatments should think very carefully about the risks. There are many untrustworthy clinics offering expensive stem cell treatments and some patients have experienced horrifying complications. Dr. Paul Knoepfler of UC-Davis has written a practical and scientifically accurate guide[vi], a strongly recommended read if you or a family member are considering treatment or a clinical trial.

[vi]https://ipscell.com/patients-guide-to-stem-cell-treatments/

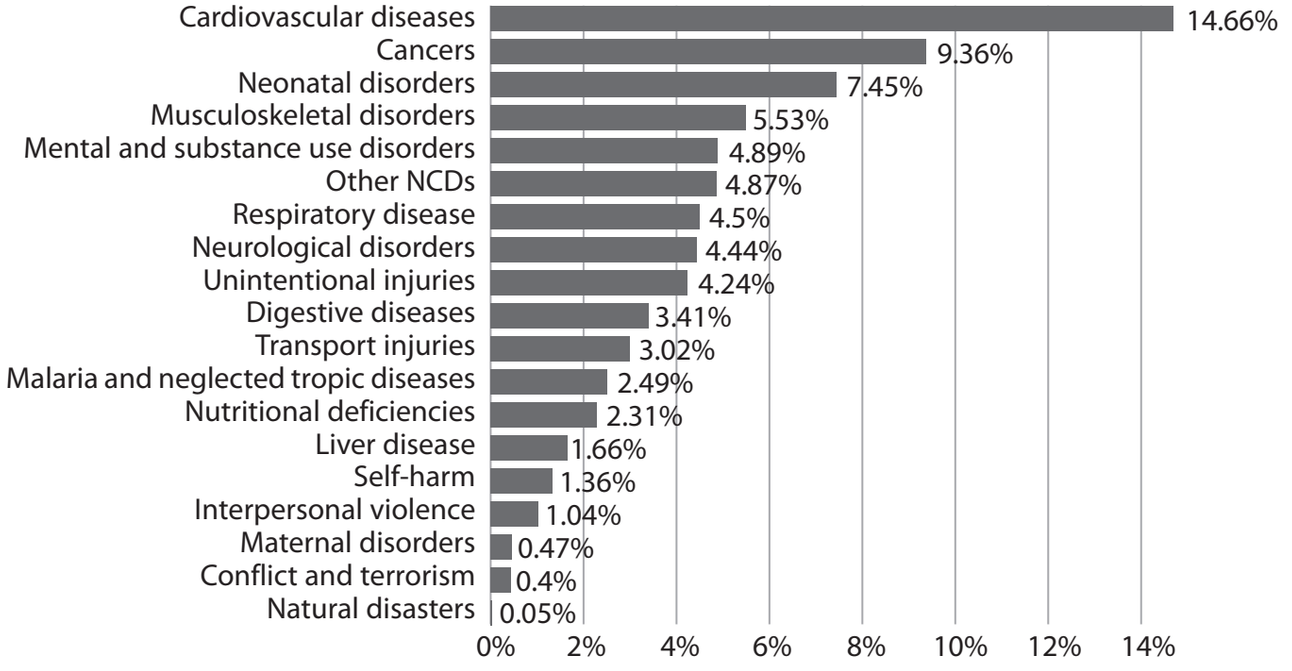
Why stem cells? Why now?

The leading causes of death in 1900 were mostly infectious/communicable diseases[vii]. While the prevalence (number of cases in a population at a specific time) of most infections has decreased, the largest increases include heart disease (+40%) and cancer (+300%). It is true that this is partly due to doubling life expectancy and a lack of death from other causes. However, given time and resources, scientists and doctors may cure these challenging diseases.

[vii]https://www.nejm.org/doi/full/10.1056/NEJMp1113569

Share of total disease burden by cause, World, 2017

Total disease burden, measured in Disability-Adjusted Life Years (DALYs) by sub-category of disease or injury. DALYs measure the total burden of disease – both from years of life lost due to premature death and years lived with a disability. One DALY equals one lost year of healthy life.



(Source: IHME, Global Burden of Diseases
OurWorldInData.org/burden-of-disease • CC BY)

Figure 1

Today, six of the seven leading causes of death are non-communicable diseases (NCDs e.g. heart disease, stroke, lung diseases, cancer, Alzheimer's disease and diabetes). Based on the early promise mentioned above, regenerative medicine may be our best hope to solve the great non-communicable diseases of our time, and perhaps the single most transformative medical innovation in a century[(viii)].

[(viii)]https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Article 3

Current state of stem cell-based therapies: an overview

This is an edited version of an article published by the National Center for Biotechnology Information in May 2020. The article was written by Riham Mohamed Aly.

Introduction

Recent research reporting successful translation of stem cell therapies to patients has enriched the hope that such regenerative strategies may one day become a treatment for a wide range of hard-to-treat diseases. In fact, the past few years witnessed, an exponential increase in clinical trials revolving around stem cell-based therapies. Some of these trials resulted in remarkable impact on various diseases. In this review, the advances and challenges for the development of stem-cell-based therapies are described, with focus on the use of stem cells in dentistry in addition to the advances achieved in regenerative treatment modalities in several diseases. The limitations of these treatments and ongoing challenges in the field are also discussed while shedding light on the ethical and regulatory challenges in translating autologous stem cell-based interventions, into safe and effective therapies.

Cell-based therapy, an example of regenerative medicine, is considered one of the most promising disciplines in the areas of modern science and medicine. Such an advanced technology offers endless possibilities for potential cures for some of the most life-threatening diseases. Regenerative medicine is rapidly becoming the next big thing in health care with the particular aim of repairing and possibly replacing diseased cells, tissues or organs and eventually getting back to normal function. The prospect of regenerative medicine as an alternative to conventional drug-based therapies is becoming a reality owing to the vigorous commitment of the research communities in studying the potential applications across a wide range of diseases including neurodegenerative diseases and diabetes (1).

Recent research reporting successful stem cell therapies has enriched the hope that such regenerative strategies may one day become a treatment for a wide range of diseases (2). In fact, the past few years have seen an exponential advancement in clinical trials to do with stem cell-based therapies. Some of these trials resulted in remarkable impacts on various diseases (3). For example, a case of Epidermolysis Bullosa (EB) where the outer layer of skin does not properly adhere to the underlying layer, showed signs of skin recovery after treatment with cultures of skin stem cells (4). Also, a major improvement in eyesight of patients suffering from macular degeneration was reported after transplantation of patient-derived induced pluripotent stem cells (iPSCs) that were induced to differentiate into cells of the retina (5).

However, in spite of the increased amount of publications reporting successful cases of stem cell-based therapies, a major number of clinical trials have not yet acquired full regulatory approvals for validation as stem cell therapies. To date, the most established stem cell treatment is bone marrow transplants to treat blood and immune system disorders (1,6,7).

In this review, the advances and challenges for the development of stem-cell-based therapies are described, with focus on the use of stem cells in dentistry in addition to the advances reached in regenerative treatments in several diseases. The limitations of these treatments and ongoing challenges in the field are also discussed while considering the ethical and regulatory challenges in going from patient-derived stem cell-based interventions, into safe and effective therapies.

Stem cell-based therapies

Stem cell-based therapies are defined as any treatment for a disease or a medical condition that involves the use of any type of human stem cell. Stem cells offer the perfect solution when there is a need for tissue and organ transplantation because they can differentiate into the specific cell types that are required for repair of diseased tissues.

However, the complexity of stem cell-based therapies often leads researchers to search for stable, safe and easily accessible stem cell sources that have the potential to differentiate into several cell types. Thus, it is of utmost importance to carefully select the type of stem cells that is most suitable for clinical application (7,9).

Stem cells hierarchy

There are mainly three types of stem cells. All three of them share the significant property of self-renewal (continued ability to divide) in addition to a unique ability to differentiate. However, it should be noted that stem cells are not all the same. Some have more potential than others so there is a hierarchy (10). The most undeveloped stem cells are the totipotent stem cells. These cells are capable of developing into a complete embryo and the extra-embryonic tissue e.g. the placenta. This unique property lasts for about 5 days; it starts with the fertilisation of the ovum and ends when the embryo reaches the four to eight cells stage. Following that stage, cells undergo more divisions until reaching the blastocyst (ball of cells) stage where they lose their totipotency property and develop a pluripotent identity where cells are only capable of differentiating into the three layers that will give rise to all the body tissues and organs. Cells of this stage are termed "embryonic stem cells (EPCs)" and are obtained by isolation from the inner cell mass of the blastocyst. This involves the destruction of the embryo. After consecutive divisions of these cells they are no longer pluripotent and their ability to differentiate becomes more restricted. The cells become multipotent (MSCs) meaning that they can only differentiate into limited types of cells related to the tissue of origin. This is the property of "adult stem cells", which are in all tissues, normally metabolically inactive, and help repair damaged tissues and replace dead cells throughout the lifetime of the organism. They include bone marrow and dental tissues among many others (11).

To many scientists adult stem cells are the best in stem cell-based therapies (12,13). Adult stem cells have demonstrated signs of clinical success especially in bone marrow transplants (14,15). In contrast to ESCs, adult stem cells are not subject to ethical or religious worries about where the cells come from. The fact that obtaining ESCs involves destruction of human embryos makes them unacceptable for a significant proportion of the population for ethical or religious reasons (16–18).

Turning point in stem cell research

In 2006 Shinya Yamanaka achieved a scientific breakthrough in stem cell research by generating cells that have the same properties and genetic profile of ESCs. He reprogrammed differentiated cells, obtained from connective tissue, into undifferentiated stem cells. He did this by adding four transcription factors. These transcription factors could switch back on genes that had been switched off during differentiation (19,20). These cells were called iPSCs (induced pluripotent stem cells) and Yamanaka's work has transformed the field of stem cell research (21). The most important feature of these cells is their ability to differentiate into any type of body cell, just like ESCs but without the ethical objections. Since they can be generated from the patient's own cells, iPSCs are a good possibility for the production of pluripotent patient-derived, matched cells that could be used for transplantation back into the patient. Nevertheless, a number of challenges still need to be investigated and addressed before iPSCs can be applied in cell therapies. Such challenges include; the detection and removal of incompletely differentiated cells and overcoming the tumorigenicity (potential to cause cancer) of these cells that could happen on transplantation (22).

Therapeutic translation of stem cell research

At the moment, some stem cell-based therapies using adult stem cells are clinically available and mainly include bone marrow transplants and skin grafts for severe burns (23). Up to the time of writing this article, there are more than 3,000 trials involving the use of adult stem cells registered in the World Health Organization (WHO) International Clinical Trials Registry.

In fact, the first clinical attempt using iPSCs reported successful results in treating the degenerative sight loss condition called macular degeneration (24). The outcomes of such trials will help the understanding of the timeframes needed to achieve successful therapies and also help gain a better understanding of the diseases. However, evaluation of stem cell-based therapies is not an easy task since transplantation of cells may result in tumour formation and other complications. This accounts for the variations in the results reported. The following section discusses the published data of some of the most important clinical trials involving the use of different types of stem cells both in medicine and in dentistry.

Stem cell-based therapy for neurodegenerative diseases

These include Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS) – a type of motor neurone disease, and multiple sclerosis (MS).

Parkinson's disease (PD)

PD is characterised by a rapid loss of brain neurones that produce the neurotransmitter dopamine. The first attempt to treat PD used human ESC cells. To avoid ethical controversies, the use of iPSCs was proposed (27).

In August 2018, Shinya Yamanaka initiated the first approved clinical trial to treat PD using iPSCs. Seven patients suffering from moderate PD were recruited (29). The trial involved the production of neurones able to produce dopamine and then the surgical transplantation of these neurones into the brains of the patients. In addition, immunosuppressant drugs were given to avoid rejection. Preliminary results so far showed the treatment to be safe.

Multiple sclerosis (MS)

MS is an inflammatory and neurodegenerative autoimmune (the patient's immune system attacks their own tissues) disease of the central nervous system. Stem cell-based therapies are now exploring the possibility of halting the disease progression and of reversing the damage to nerves. A registered phase 1 clinical trial was carried out by the company Celgene™ in 2014 using adult stem cells to treat patients suffering from MS (30). This trial was performed at 6 centres in the United States and 2 centres in Canada and included 16 patients. Results demonstrated that the treatment was safe. However, clinical responses from patients indicated that the treatment did not improve the MS condition (31). A therapy that involves removing the patient's immune system and replacing it with a bone marrow transplant has led to remission (relief from the symptoms) (32). However, some patients suffered complications such as infertility and neurological disabilities. A number of randomised controlled trials are planned to answer these concerns (32). Currently, new and innovative stem cell-based therapies for MS are only in the initial stages, and are based on the possibility of replacing damaged nerve tissue with nerve cells derived from iPSCs. However, the potential of using iPSCs in treatments is still the subject of research (33).

Spinal cord injury

Stem cells have the potential to treat spinal cord injuries. The transplantation of different forms of nerve stem cells has led to growth in the axons of neurones as well as to an increase in connections between neurones (36). However, proof of recovered function has yet to be shown in clinical trials. Nevertheless, Japan has recently given approval to stem-cell treatment for spinal-cord injuries. This approval was based on clinical trials that are yet to be published and involve 13 patients, who are suffering from recent spinal-cord injury. The Japanese team discovered that injection of stem cells isolated from the patients' bone marrow led to them gaining some sensation and mobility.

This is the first stem cell-based therapy targeting spinal-cord injuries to gain government approval to offer to patients (37).

Stem cell-based therapies for ocular (eye) diseases

A huge number of the currently registered clinical trials for stem cell-based therapies target eye diseases. This is mainly due to the fact that many parts of the eye are out of reach of the immune system. Most of these trials are happening in various countries including Japan, China, Israel, Korea, UK, and USA and they use ESCs from donors (35,36).

Notably, the first clinical trial to introduce the use of patient-derived iPSCs to make retinal cells for transplantation was in Japan. It followed the new regulatory laws issued in 2014 by Japan's government to regulate regenerative medicine applications. Two patients were recruited in this trial; the first one received treatment for macular degeneration using retinal cells generated from iPSCs (37). After 1 year of follow-up, there were no signs of serious complications or tumours. Moreover, there were no signs of rejection of the transplanted cells in the second year follow-up. Most importantly, the patients reported improvement in their vision. These results were enough to conclude that iPSCs-based transplantation was safe and possible (38).

Stem cell-based therapies for treatment of diabetes

Pancreatic beta cells are destroyed in type 1 diabetes mellitus, because of disorders in the immune system. It is an autoimmune disease. Type 2 diabetes is caused by failure of the beta-cells to produce enough insulin and a failure of insulin receptors on cells to detect and respond to the insulin. Several genes are involved and also many environmental factors and type 2 diabetes can be prevented or reversed with changes in lifestyle.

In both cases the affected cells are the beta cells in the islets of Langerhans and, since the pancreas does not efficiently regenerate islets from endogenous adult stem cells, other cell sources were tested (38). Pluripotent stem cells (PSCs) are considered the cells of choice for beta cell replacement strategies (39). At the moment, there are a few clinical trials targeting beta cell replacement using ESCs. These trials involve the insertion of insulin-producing beta cells, in a capsule, under the skin (40). The company ViaCyte™ in California initiated a trial* in 2014 in collaboration with Harvard University.
*https://clinicaltrials.gov/ct2/show/NCT02239354

This involved 40 patients and used two capsules of insulin-producing beta cells generated from ESCs. This demonstrated successful blood glucose level regulation. The capsules were taken out after 174 days and found to contain insulin-producing cells (41).

Stem cells in dentistry

MSCs have been isolated from dental tissues such as dental pulp (the central part) of adult and infant teeth and surrounding tissues (42–44). These cells were described as an excellent cell source owing to their ease of accessibility, their ability to differentiate into bone-forming cells and tooth-forming cells and for their lack of ethical controversies (45). However, assessments of stem cells after transplantation still require extensive studying. The results of clinical trials have yet to be fully evaluated. However, stem cell-based dental regeneration may soon be a readily available treatment.

Dental pulp regeneration

The first human clinical study using patient-derived dental pulp stem cells (DPSCs) for complete pulp regeneration was reported by Nakashima et al. in 2017 (49). Patients with irreversible pulpitis (inflammation of the pulp cavity) were recruited and followed up for 6 months following DPSCs transplantation. The research team reported that the use of DPSCs seeded on collagen (a protein found in many body tissues) – the connective tissue scaffold in molars and premolars, was safe. No harmful events or toxicity were demonstrated. Magnetic resonance imaging (MRI scans) of the new tissues formed in the root canal showed successful pulp regeneration. A different group conducted a clinical trial where patient-derived stem cells from their infant teeth were employed to induce pulp regeneration (51). Follow-up of the cases a year after the intervention reported evidence of pulp regeneration with new blood and nerve supplies. In addition, no signs of adverse effects were observed. Both trials are proceeding with the next phases. The results obtained are promising.

Regeneration of mandibular (jaw) bony defects

The first clinical study using DPSCs for facial bone regeneration was conducted in 2009 (53). Patients in this study suffered from extreme bone loss following extraction of wisdom teeth. Three years later, the same group published a report evaluating the stability and quality of the regenerated bone after DPSCs transplantation (54). The newly formed bone was uniformly vascularised (supplied with blood vessels). However, it was of compact bone rather than spongy bone, which is usually the type of bone in this region.

Stem cells and tissue banks

The ability to bank stem cells at their most potent state for later use is essential for stem cell-based therapies. In order to be considered valid, any new stem cell-based therapy should be as effective as the routine treatment. When evaluating a type of stem cell for use in cellular therapies, issues such as immune rejection must be avoided and, at the same time, large numbers of stem cells must be readily available before clinical use. iPSCs theoretically possess the ability for unlimited division which makes them an attractive source for use in cell-based therapies. Unlike adult stem cells, the ability of iPSCs to continue to divide does not decrease with time (22). Recently, California Institute for Regenerative Medicine (CIRM) has introduced an iPSCs bank to provide researchers with iPSCs cell lines in order to accelerate stem cell treatments through studying genetic variation and disease modelling.

Another important source for stem cells banking is the umbilical cord. Umbilical cord is immediately preserved at low temperature after birth, which permits stem cells to be successfully stored and be ready for use in cell-based therapies for incurable diseases. However, stem cells from human infant teeth are more attractive as a source for stem cell banking. These cells have the capacity to differentiate into more cell types than the rest of the adult stem cells can (56). Moreover, procedures involving the isolation and freezing of these cells are uncomplicated. The most important advantage of banking infant teeth for specific individuals is for transplants that avoid the possibility of rejection (57). Unlike cord blood stem cells, teeth stem cells have the ability to differentiate into connective tissues, neural and dental tissues (58). Finally, the ultimate goal of stem cell banking, is to establish a repository of high-quality stem cell lines derived from many individuals for future use in therapy.

Current regulatory guidelines for stem cell-based therapies

With the increased number of clinical trials employing stem cells, the need for developing regulatory guidelines and standards to ensure patient safety is becoming more and more essential. However, the fact that stem cell therapy is rather a new area makes it subject to scientific, ethical and legal controversies that are yet to be regulated. Leading countries in the field have devised guidelines for that purpose. In the USA, the Food and Drug Administration (FDA) has released regulatory guidelines to ensure that these treatments are safe and effective (59). In 2014, a radical regulatory reform in Japan occurred with the passing of two new laws that permitted conditional approval of cell-based treatments following early phase clinical trials on the condition that clinical safety data are provided from at least ten patients. These laws allow skipping most of the traditional criteria of clinical trials in what was described as "fast track approvals" and treatments were classified according to risk (60). To date, the treatments that acquired conditional approval include those targeting spinal-cord injury and cardiac disease (61).

Challenges and ethical issues facing stem cell-based therapies

Stem cell-based therapies face many obstacles that need to be urgently addressed. The most persistent concern is the ethical conflict regarding the use of ESCs. As previously mentioned, ESCs are far superior regarding their potency; however, obtaining them requires destruction of human embryos, obtained from spare embryos created during IVF treatments. True, the discovery of iPSCs overcame this concern. Nevertheless, iPSCs themselves currently face another ethical controversy which addresses their unlimited capacity of differentiation with concerns that these cells could one day be used for human cloning. The use of iPSCs in therapy is still considered a high-risk treatment, since transplantation of these cells could induce tumour (cancer) formation. Such challenge is currently addressed through developing protocols to ensure their safety in addition to developing global clinical-grade iPSCs cell lines before these cells are available for clinical use (61). As for MSCs, these cells have been universally considered safe. However, continuous monitoring and prolonged follow-up should be the focus of future research to avoid the possibility of tumour formation after treatments (62).

Finally, it could be proposed that one of the most challenging ethical issues, faced in the field of stem cell-based therapies at the moment, is the increasing number of clinics offering unproven stem cell-based treatments. Researchers are thus morally obliged to ensure that ethical considerations are not undermined in trying to make progress in clinical use.

Conclusions

Stem cell therapy is becoming a reality by the day, thanks to the increasing amount of research conducted over the past decade. With every research conducted the possibilities of stem cell applications increased in spite of the many challenges faced. Currently, progress in the area of stem cells is very promising with reports of clinical success in treating various diseases such as neurodegenerative diseases and macular degeneration, progressing rapidly. iPSCs are conquering the field of stem cell research with endless possibilities of treating diseases using patients' own cells. Regeneration of dental tissues has made its way to the clinic and soon enough will become a valid treatment. Although challenges might seem daunting, stem cell research is advancing rapidly and cellular therapies will soon be used. Fortunately, there are currently tremendous efforts exerted globally towards setting up regulatory guidelines and standards to ensure patient safety. In the near future, stem cell-based therapies shall significantly improve human health.

References

This article has been edited and some references have been removed from the list.

1. Chari S, Nguyen A, Saxe J. Stem Cells in the Clinic. *Cell Stem Cell* 2018;22:781–2. 10.1016/j.stem.2018.05.017 [PubMed] [CrossRef] [Google Scholar]

2. Madl CM, Heilshorn SC, Blau HM. Bioengineering strategies to accelerate stem cell therapeutics. *Nature* 2018;557:335–42. 10.1038/s41586-018-0089-z [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Pérez López S, Otero Hernández J. Advances in stem cell therapy. *Adv Exp Med Biol* 2012;741:290–313. 10.1007/978-1-4614-2098-9_19 [PubMed] [CrossRef] [Google Scholar]

4. Hirsch T, Rothoeft T, Teig N, et al. Regeneration of the entire human epidermis using transgenic stem cells. *Nature* 2017;551:327-32. 10.1038/nature24487 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Mandai M, Kurimoto Y, Takahashi M. The authors reply. Vol. 377, *New England Journal of Medicine*. Massachusetts Medical Society, 2017:792–3. [Google Scholar]

6. Trounson A, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. *Cell Stem Cell* 2015;17:11–22. 10.1016/j.stem.2015.06.007 [PubMed] [CrossRef] [Google Scholar]

7. De Luca M, Aiuti A, Cossu G, et al. Advances in stem cell research and therapeutic development. *Nat Cell Biol* 2019;21:801–11. 10.1038/s41556-019-0344-z [PubMed] [CrossRef] [Google Scholar]

9. Bobba S, Di Girolamo N, Munsie M, et al. The current state of stem cell therapy for ocular disease. *Exp Eye Res* 2018;177:65–75. 10.1016/j.exer.2018.07.019 [PubMed] [CrossRef] [Google Scholar]

10. Gaskell T, Englund MCO, Hyllner J. Human embryonic stem cells. In: Steinhoff G. editor. Regenerative Medicine – from Protocol to Patient: 2. Stem Cell Science and Technology. 3rd edition. Springer, 2016. [Google Scholar]

11. Clevers H, Watt FM. Defining Adult Stem Cells by Function, not by Phenotype. *Annu Rev Biochem* 2018;87:1015–27. 10.1146/annurev-biochem-062917-012341 [PubMed] [CrossRef] [Google Scholar]

12. Prentice DA. Adult Stem Cells. *Circ Res* 2019;124:837–9. 10.1161/CIRCRESAHA.118.313664 [PubMed] [CrossRef] [Google Scholar]

13. Lukomska B, Stanaszek L, Zuba-Surma E, et al. Challenges and Controversies in Human Mesenchymal Stem Cell Therapy. *Stem Cells Int* 2019;2019:9628536. [PMC free article] [PubMed]

14. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. *Nature* 2014;505:327–34. 10.1038/nature12984 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

15. Sharpe M, Leoni G, Hyllner J. Stem Cells. In: McQueen CA. Comprehensive Toxicology. 3rd edition. Elsevier, 2017:23–59. [Google Scholar]

16. Green RM. Ethical Considerations. In: Lanza R, Atala A. editors. Essentials of Stem Cell Biology. 3rd edition. Elsevier, 2013:595–604. [Google Scholar]

17. Brignier AC, Gewirtz AM. Embryonic and adult stem cell therapy. *J Allergy Clin Immunol* 2010;125:S336–44. 10.1016/j.jaci.2009.09.032 [PubMed] [CrossRef] [Google Scholar]

18. Lo B, Parham L. Ethical issues in stem cell research. *Endocr Rev* 2009;30:204–13. 10.1210/er.2008-0031 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

19. Takahashi K, Yamanaka S. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell* 2006;126:663–76. 10.1016/j.cell.2006.07.024 [PubMed] [CrossRef] [Google Scholar]

20. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell* 2007;131:861–72. 10.1016/j.cell.2007.11.019 [PubMed] [CrossRef] [Google Scholar]

21. Shi Y, Inoue H, Wu JC, et al. Induced pluripotent stem cell technology: a decade of progress. *Nat Rev Drug Discov* 2017;16:115–30. 10.1038/nrd.2016.245 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

22. Attwood SW, Edel MJ. iPS-Cell Technology and the Problem of Genetic Instability–Can It Ever Be Safe for Clinical Use? *J Clin Med* 2019;8:288. 10.3390/jcm8030288 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

23. Poulos J. The limited application of stem cells in medicine: a review. *Stem Cell Res Ther* 2018;9:1. 10.1186/s13287-017-0735-7 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

24. Mandai M, Watanabe A, Kurimoto Y, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. *N Engl J Med* 2017;376:1038–46. 10.1056/NEJMoa1608368 [PubMed] [CrossRef] [Google Scholar]

27. Kikuchi T, Morizane A, Doi D, et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. *Nature* 2017;548:592–6. 10.1038/nature23664 [PubMed] [CrossRef] [Google Scholar]

29. Takahashi J. Stem cell therapy for Parkinson's disease. *Expert Rev Neurother* 2007;7:667–75. 10.1586/14737175.7.6.667 [PubMed] [CrossRef] [Google Scholar]

30. Lublin FD, Bowen JD, Huddlestone J, et al. Human placenta-derived cells(pda-001) for the treatment of adults with multiple sclerosis: A randomized, placebo-controlled, multiple-dose study. *Mult Scler Relat Disord* 2014;3:696–704. 10.1016/j.msard.2014.08.002 [PubMed] [CrossRef] [Google Scholar]

31. Cuascut FX, Hutton GJ. Stem Cell-Based Therapies for Multiple Sclerosis: Current Perspectives. *Biomedicines* 2019;7:26. 10.3390/biomedicines7020026 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

32. Delemarre EM, Van Den Broek T, Mijnheer G, et al. Autologous stem cell transplantation AIDS autoimmune patients by functional renewal and TCR diversification of regulatory T cells. *Blood* 2016;127:91–101. 10.1182/blood-2015-06-649145 [PubMed] [CrossRef] [Google Scholar]

33. Thiruvalluvan A, Czepiel M, Kap YA, et al. Survival and Functionality of Human Induced Pluripotent Stem Cell-Derived Oligodendrocytes in a Non-human Primate Model for Multiple Sclerosis. *Stem Cells Transl Med* 2016;5:1550–61. 10.5966/sctm.2016-0024 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

35. Mazzini L, Ferrari D, Andjus PR, et al. Advances in stem cell therapy for amyotrophic lateral sclerosis. *Expert Opin Biol Ther* 2018;18:865–81. 10.1080/14712598.2018.1503248 [PubMed] [CrossRef] [Google Scholar]

36. Assinck P, Duncan GJ, Hilton BJ, et al. Cell transplantation therapy for spinal cord injury. *Nat Neurosci* 2017;20:637–47. 10.1038/nn.4541 [PubMed] [CrossRef] [Google Scholar]

37. Cyranoski D. Japan's approval of stem-cell treatment for spinal-cord injury concerns scientists. *Nature* 2019;565:544–5. 10.1038/d41586-019-00178-x [PubMed] [CrossRef] [Google Scholar]

38. Dor Y, Brown J, Martinez OI, et al. Adult pancreatic β-cells are formed by self-duplication rather than stem-cell differentiation. *Nature* 2004;429:41–6. 10.1038/nature02520 [PubMed] [CrossRef] [Google Scholar]

39. Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells *in vitro. Cell* 2014;159:428–39. 10.1016/j.cell.2014.09.040 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

40. Schulz TC, Young HY, Agulnick AD, et al. A scalable system for production of functional pancreatic progenitors from human embryonic stem cells. *PLoS One* 2012;7:e37004. 10.1371/journal.pone.0037004 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

41. Vegas AJ, Veiseh O, Gürtler M, et al. Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice. Nat Med 2016;22:306–11. 10.1038/nm.4030 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

42. Raspini G, Wolff J, Helminen M, et al. Dental Stem Cells Harvested from Third Molars Combined with Bioactive Glass Can Induce Signs of Bone Formation *In Vitro*. *J Oral Maxillofac Res* 2018;9:e2. 10.5037/jomr.2018.9102 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

43. Yasui T, Mabuchi Y, Morikawa S, et al. Isolation of dental pulp stem cells with high osteogenic potential. *Inflamm Regen* 2017;37:8. 10.1186/s41232-017-0039-4 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

44. Suchánek J, Visek B, Soukup T, et al. Stem cells from human exfoliated deciduous teeth-isolation, long term cultivation and phenotypical analysis. *Acta Medica* (*Hradec Kralove*) 2010;53:93–9. 10.14712/18059694.2016.66 [PubMed] [CrossRef] [Google Scholar]

45. Hu L, Liu Y, Wang S. Stem cell-based tooth and periodontal regeneration. *Oral Dis* 2018;24:696–705. 10.1111/odi.12703 [PubMed] [CrossRef] [Google Scholar]

49. Nakashima M, Iohara K, Murakami M, et al. Pulp regeneration by transplantation of dental pulp stem cells in pulpitis: a pilot clinical study. *Stem Cell Res Ther* 2017;8:61. 10.1186/s13287-017-0506-5 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

51. Xuan K, Li B, Guo H, et al. Deciduous autologous tooth stem cells regenerate dental pulp after implantation into injured teeth. *Sci Transl Med* 2018;10:eaaf3227. [PubMed]

53. d'Aquino R, De Rosa A, Lanza V, et al. Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes. *Eur Cell Mater* 2009;18:75–83. 10.22203/eCM.v018a07 [PubMed] [CrossRef] [Google Scholar]

54. Giuliani A, Manescu A, Langer M, et al. Three Years After Transplants in Human Mandibles, Histological and In-Line Holotomography Revealed That Stem Cells Regenerated a Compact Rather Than a Spongy Bone: Biological and Clinical Implications. *Stem Cells Transl Med* 2013;2:316–24. 10.5966/sctm.2012-0136 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

56. Ma L, Makino Y, Yamaza H, et al. Cryopreserved Dental Pulp Tissues of Exfoliated Deciduous Teeth Is a Feasible Stem Cell Resource for Regenerative Medicine. *PLoS One* 2012;7:e51777. 10.1371/journal.pone.0051777 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

57. Arora V, Arora P, Munshi AK. Banking stem cells from human exfoliated deciduous teeth (SHED): saving for the future. *J Clin Pediatr Dent* 2009;33:289–94. 10.17796/jcpd.33.4.y887672r0j703654 [PubMed] [CrossRef] [Google Scholar]

58. Cordeiro MM, Dong Z, Kaneko T, et al. Dental Pulp Tissue Engineering with Stem Cells from Exfoliated Deciduous Teeth. *J Endod* 2008;34:962–9. 10.1016/j.joen.2008.04.009 [PubMed] [CrossRef] [Google Scholar]

59. Marks PW, Witten CM, Califf RM. Clarifying Stem-Cell Therapy's Benefits and Risks. *N Engl J Med* 2017;376:1007–9. 10.1056/NEJMp1613723 [PubMed] [CrossRef] [Google Scholar]

60. Konomi K, Tobita M, Kimura K, et al. New Japanese initiatives on stem cell therapies. *Cell Stem Cell* 2015;16:350–2. 10.1016/j.stem.2015.03.012 [PubMed] [CrossRef] [Google Scholar]

61. Cyranoski D. The potent effects of Japan's stem-cell policies. *Nature* 2019;573:482–5. 10.1038/d41586-019-02847-3 [PubMed] [CrossRef] [Google Scholar]

62. Volarevic V, Markovic BS, Gazdic M, et al. Ethical and safety issues of stem cell-based therapy. *Int J Med Sci* 2018;15:36–45. 10.7150/ijms.21666 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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Please check the examination details below before entering your candidate information

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Pearson BTEC Level 3 Nationals Extended Diploma

Supervised hours: 2 hours 30 minutes

Paper reference **31629H**

Applied Science

UNIT 7: Contemporary Issues in Science

Part B

You will need:
Up to four sides of A4 notes from **Part A**

Total Marks

Instructions

- Use **black** ink or ball-point pen.
- **Fill in the boxes** at the top of this page with your name, centre number and learner registration number.
- Answer **all** questions.
- Answer the questions in the spaces provided – *there may be more space than you need*.
- **Part A** will need to have been used in preparation for completion of **Part B**.
- **Part B** must be undertaken in a single session of 2 hours and 30 minutes in the assessment session timetabled by Pearson.
- **Part B** materials must be issued by learners for the specified session.
- **Part B** is specific to each series and this material must only be issued to learners who have been entered to undertake the task in the relevant series.
- **Part B** should be kept securely until the start of the 2 hour and 30 minute supervised assessment.

Information

- The total mark for this paper is 50.
- The marks for **each** question are shown in brackets – *use this as a guide as to how much time to spend on each question*.
- The three articles are at the back of **Part B**.

Advice

- Read each question carefully before you start to answer it.
- Try to answer every question.
- Check your answers if you have time at the end.

Turn over ▶

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Instructions to Teachers/Tutors

This paper must be read in conjunction with the unit information in the specification and the *BTEC Nationals Instructions for Conducting External Assessments* (ICEA) document. See the Pearson website for details.

Part B set task is undertaken under supervision in a single session of 2 hours and 30 minutes in the timetabled session.

Part B set task requires learners to apply understanding gained through familiarisation with the articles. Learners should bring in notes as defined in **Part A**.

Learners must complete the set task using this task and answer booklet.

Maintaining security

- Only permitted materials for the set task can be brought into the supervised environment.
- During any permitted break and at the end of the session materials must be kept securely and no items removed from the supervised environment.
- Learner notes related to **Part A** must be checked to ensure length and contents meet limitations.
- Learner notes from **Part A** will be retained securely by the centre after **Part B** and may be requested by Pearson if there is suspected malpractice.

After the session the teacher/tutor and/or invigilator will confirm that all learner work was completed independently as part of the authentication submitted to Pearson.

Outcomes for submission

This task and answer booklet should be submitted to Pearson.

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Instructions for Learners

Read the set task information carefully.

Complete all your work in this task and answer booklet in the spaces provided.

This session is of 2 hours 30 minutes (during the day). Plan your time carefully.

You have prepared for the set task given in this **Part B** task and answer booklet. Use your notes prepared during **Part A** if relevant. Attempt all the questions in **Part B**.

Your notes must be your own work and will be retained by your centre until results are issued.

You will complete this set task under supervision and your work will be kept securely during any breaks taken.

You must work independently throughout the supervised assessment period and must not share your work with other learners.

Outcomes for submission

You will need to submit the following document on completion of the supervised assessment period:

- a completed **Part B** task and answer booklet.

Set Task

Answer ALL questions in the spaces provided.

1 Discuss the implications of the scientific issue identified in the articles.

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(Total for Question 1 = 12 marks)

2 Identify the different organisations/individuals mentioned in the articles and suggest how they may have an influence on the scientific issue.

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(Total for Question 2 = 6 marks)

3 Discuss whether Article 3 has made valid judgements.

In your answer you should consider:

- how the article has interpreted and analysed the scientific information to support the conclusions/judgements being made
- the validity and reliability of the data
- references to other sources of information.

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(Total for Question 3 = 12 marks)

4 Suggest potential areas for further development and/or research of the scientific issue from the three articles.

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(Total for Question 4 = 5 marks)

5 You are a trainee technician in a laboratory.

The scientists in the laboratory are carrying out research into stem cell therapy.

You have been asked to write an article for a youth science magazine about the benefits and possible risks of stem cell therapy.

Teenagers who are interested in stem cell therapy will read the article.

Use information from the three articles provided for this task.

When writing your article you should consider:

- who is likely to read the article and how you can present the information in a clear and accessible way
- what you would like the reader to learn from the article.

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(Total for Question 5 = 15 marks)

TOTAL FOR PAPER = 50 MARKS

Part A Set Task Information

Article 1

How stem cell research could help repair heart attack damage

This is an edited version of an article published on the British Heart Foundation website on May 2021.

Professor Ian Wilmut stands beside Dolly the sheep, the world's first cloned animal.
(Source: © PA Images/Alamy Stock Photo)

Stem cell research could reveal new ways to help us mend broken hearts, as Sarah Kidner discovers.

Chances are you've heard of stem cells. Even if you haven't, you'll know of Dolly the cloned sheep – the original 'poster girl' of this sensational field of scientific research.

Twenty-five years ago, Dolly's creation saw scientists accused of 'playing God', but while stem cell research does raise ethical questions, it may also hold the answer to mending hearts damaged by a heart attack and has many other potential uses.

Two professors working in the newest areas of stem cell research tell us how their work could affect people's lives in the future.

"It's an amazing breakthrough." says Chris Denning, Professor of Stem Cell Biology at the University of Nottingham. "Ten years ago, we couldn't have conceived of these studies, but what was once impossible is now possible."

He's referring to induced pluripotent stem (iPS) cells. Their development won Shinya Yamanaka and John Gurdon the Nobel Prize for Physiology or Medicine in 2012. But what are iPS cells, and why is this type of research so important?

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iPS cells explained

Until recently, to do stem cell research scientists needed to obtain human embryonic stem cells from spare IVF (*in vitro* fertilisation) embryos with the permission of the donors. These embryonic cells could be stimulated into becoming any type of human body cell.

Today, you can simply take a skin biopsy or a blood sample from a patient to obtain cells. By adding four factors to switch on four genes, these cells are genetically reprogrammed to become stem cells.

"The four factors are called the Yamanaka factors, after Shinya Yamanaka", explains Professor Denning. The beauty of the iPS cell technique is that it is so simple.

"Everybody thought Yamanaka was crazy when he presented iPS cells at a big international conference. Within a year several labs had repeated the technique. Yamanaka was a superstar; the Japanese Government invested £65.1 million in him. Just six years later, he won the Nobel Prize."

Patient in a dish

By adding specific growth factors, you can turn iPS cells into beating heart cells in a dish. This means it's possible to study people with heart conditions without conducting invasive procedures.

"Imagine you have an inherited heart condition," says Professor Denning. "I say: 'I would like to investigate it using some of your heart cells, so I need to crack your chest open and cut out a little piece of your heart. But because the cells only last a few weeks in the lab, can I come back the next week and do the same again?' It's not going to happen."

"Now, I can take a skin biopsy, do the genetic reprogramming that turn it into stem cells and keep growing them. We're still working with the same population of cells we reprogrammed in 2008 and all we took was a skin biopsy the size of a matchstick head."

Professor Denning is able to use these iPS cells to research inherited conditions that lead to sudden death. "When patients with this condition get stressed or experience strange stimuli, they can start to experience terrible arrhythmias (irregular heartbeats) that could lead to cardiac arrest," he explains.

We are reaping the harvest of several decades of painstaking research

BHF Professor Michael Schneider

"What we're able to do in a lab is mimic the person's condition in a culture dish. This is because the cells retain the genetic abnormalities present in those who donated the skin biopsy."

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New drug therapies to regenerate dead cells?

'Patients in a dish' could also help create new drugs. "If you're a person with a condition and someone says they want to test 1,000 different drugs in you, you would say 'I think not' – some of them might be harmful," says Professor Denning. "But if you can replicate these things, you can ask if those drugs work when tested in a dish."

He says what makes this recent work worthwhile is seeing the impact it might have on people's lives. "Once in a while, you have a little bit of a breakthrough, but I have to say that the thing that made me happiest was when we published our 2011 paper. Our clinical colleagues forwarded it on to a patient's family and the father replied to thank us for the work we're doing in this area. That is why we're doing it."

When someone suffers a heart attack, cells in the heart are starved of oxygen and die. This can lead to the chronic and life-limiting condition heart failure, for which there's currently no cure.

We don't know how to mend or regenerate dead cells, but stem cell research could unlock new ways of doing precisely that.

BHF Professor Michael Schneider and his team at Imperial College London are leading research to explore how we can kick-start heart cells to regenerate or repair heart muscle following a heart attack.

Their focus is on the limited number of stem cells, which already exist within the heart muscle, and to "learn how they might contribute to heart repair in the case of injury," says Professor Schneider.

Specifically, the team aims to learn how the heart's own stem cells become more effective at creating new heart muscle following a heart attack. "Our main emphasis is on finding highly cloneable cells with the ability to become all the needed cell types in the heart," says Professor Schneider.

"It's too early to say how this might work, but it may be that doctors deliver drug-like molecules or hormones into the body to activate stem cells in the heart to become new cardiac muscle to treat heart attacks."

Understanding of these techniques is continually growing. "There has never been a better time to support the BHF than now," says Professor Schneider. "We are getting the benefit of many years of previous research. The advances and their progression into clinical treatments for patients have never happened at a faster rate."

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Using stem cells in research

The BHF supports essential research using stem cells because we believe they have the potential to cure conditions that are incurable today.

We fund research that uses stem cells from human or animal embryos and adult tissues, because we believe that both approaches are important.

Many of the advances in stem cell research have only been possible through the knowledge and insight gained using embryonic stem cells. We recognise that this is an area some people have concerns about.

Embryonic stem cells (ESCs)

Embryonic stem cells used in research are donated by couples who have undergone *in vitro* fertilisation (IVF) treatment. They choose to donate spare embryos that would otherwise be destroyed, so that stem cells can be extracted for use in research. Only embryos at a very early stage of development (up to 14 days) can be used.

We'll only fund research using embryonic stem cells where:

- the application has been through a thorough scientific review panel, to which researchers must show that this project could not be carried out in another way
- there is a licence from the Human Fertilisation and Embryology Authority (HFEA)
- there is approval from an independent research ethics committee.

More work to be done

Heart and circulatory disease kills one in four people in the UK, but stem cell research holds real promise to help us save lives in the future.

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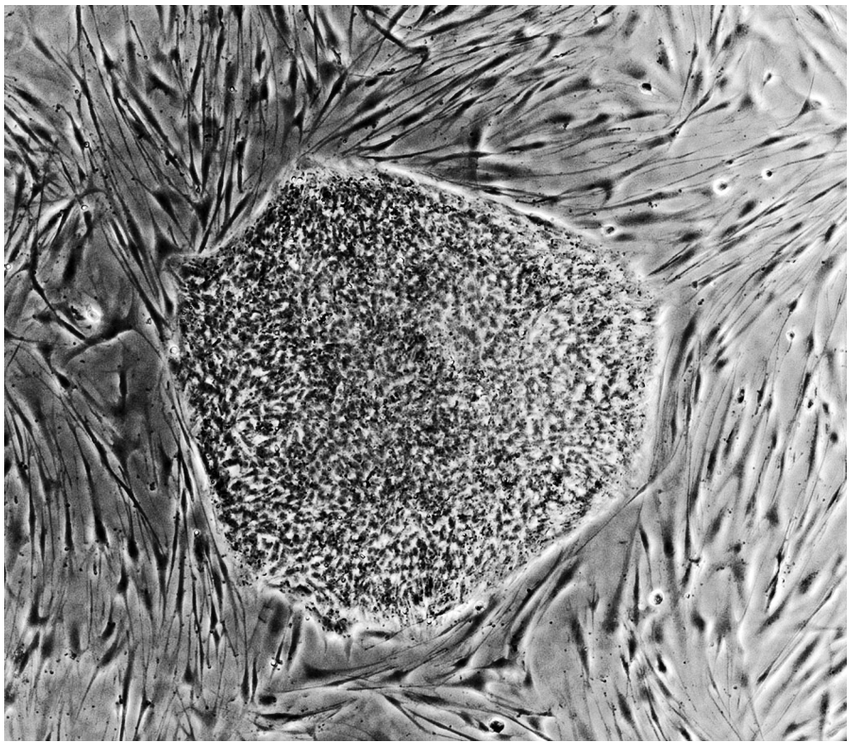
Article 2

Why stem cells could be the medical innovation of the century

This is an edited version of an article published by the World Economic Forum in January 2020. The article was written by Mike Moradi.



A colony of embryonic stem cells
(Source: © Science Source/SCIENCE PHOTO LIBRARY)

- At the moment, the demand for stem cell therapies is growing extremely quickly and will rapidly expand when a breakthrough treatment for non-communicable disease or a lifestyle factor occurs.
- Funding is flowing into the sector from investors and large companies.
- With greater resources and an increasingly experienced talent pool, scientists and doctors may be able to develop stem cell science to cure the world's most challenging diseases.

Right now, your body's stem cells are working hard replacing your skin every two weeks, creating new red and white blood cells and completing thousands of other tasks essential to life. They are your own individual way of keeping young.

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Scientists generally agree that a stem cell should be able to do both of the following:

- Self-renew: divide into another stem cell, which means making an identical copy of itself; and
- Differentiate: change into a variety of other cell types.

One theory of ageing suggests that between the ages of 30 and 50, our stem cells reach a turning point and start to decline in number and function. This results in the typical features associated with ageing.

A brief history of stem cells

There does not seem to be a single discoverer of stem cells. Accounts date back to the 1800s and even further, but the first successful medical procedure was a bone marrow transfusion[(i)] in 1939.
[(i)]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4222417/

Advances in immunology led to donor matching, initially via siblings and close relatives. Unrelated donor matching grew rapidly in the 1970s, alongside donor registries.

In the 1980s, scientists identified embryonic stem cells in mice, leading to the 1997 cloning of Dolly the sheep. This created immense interest for human and medical applications and a negative response in the US as government research and development (R&D) funding was essentially stopped in 2001.

In 2012, a Nobel Prize[(ii)] was awarded for the earlier discovery of induced pluripotent stem cells (iPS). Essentially, scientists are able to make mature cells act like stem cells again.
[(ii)]https://www.nobelprize.org/prizes/medicine/2012/press-release/

In the 10 years between 2010 and 2019, the first lot of stem cell start-up companies emerged, alongside R&D programmes at many large pharmaceutical companies, leading to innovation and the first human clinical trials for iPS and other related therapies.

Regenerative medicine in 2019

Regenerative medicine is an area of medicine that develops ways to regrow, replace or repair damaged or diseased cells, tissues or organs.

There is substantial investment in regenerative medicine across the world. According to data published in 2019, there were 959 regenerative medicine companies worldwide sponsoring 1,052 active clinical trials; 525 of these companies are in North America, 233 in Europe and Israel, and 166 in Asia. In total, $7.4 billion has been invested in regenerative medicine companies in 2019, $5.6 billion of which has been dedicated to gene and gene-modified cell therapy, $3.3 billion in cell therapy, and $114 million in tissue engineering.

Curative therapies are starting to be sold and the results are astonishing: 60% of Acute Lymphoblastic Leukaemia patients taking Novartis' Kymriah showed a complete response (no traces of cancer) and were declared in full remission. Meanwhile, 75% of patients with β-Thalassaemia treated with bluebird bio's Zynteglo achieved independence from transfusions. 93% of spinal muscular atrophy (wasting away) patients treated with Novartis' Zolgensma were alive without permanent ventilation 24 months after treatment. We should expect more medical breakthroughs in the coming years.

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What is next?

New science, new start-ups: several companies in the sector have gone from being private companies to being publicly funded. This leads to the recycling of talent and capital into new companies. Because the science and commercial systems have also advanced, the new companies are pursuing bigger challenges and driving innovation with even greater resources.

Patients are eager: the demand for stem cell therapies is growing each year, though it will rapidly expand when a breakthrough occurs toward the treatment of a non-communicable disease (such as cancer, diabetes, heart disease) or a lifestyle factor (for example, growing hair in the correct places, expanding cognitive abilities or increasing healthy lifespan).

New R&D models: funding is flowing into the sector from large companies, funds from investors, and institutions such as the California Institute for Regenerative Medicine (CIRM) and New York State Stem Cell Science programme (NYSTEM). Some of the leading university R&D organisations include the Center for the Commercialization of Regenerative Medicine[iii] in Toronto, the Stanford Institute for Stem Cell Biology and Regenerative Medicine[iv], the Oxford Stem Cell Institute, and most notably, the Harvard Stem Cell Institute (HSCI)[v].

[iii]https://www.ccrm.ca/
[iv]https://med.stanford.edu/stemcell.html
[v]https://hsci.harvard.edu/startups

Where can I get some stem cells?

Though patients' needs are immediate, those seeking treatments should think very carefully about the risks. There are many untrustworthy clinics offering expensive stem cell treatments and some patients have experienced horrifying complications. Dr. Paul Knoepfler of UC-Davis has written a practical and scientifically accurate guide[vi], a strongly recommended read if you or a family member are considering treatment or a clinical trial.

[vi]https://ipscell.com/patients-guide-to-stem-cell-treatments/

Why stem cells? Why now?

The leading causes of death in 1900 were mostly infectious/communicable diseases[vii]. While the prevalence (number of cases in a population at a specific time) of most infections has decreased, the largest increases include heart disease (+40%) and cancer (+300%). It is true that this is partly due to doubling life expectancy and a lack of death from other causes. However, given time and resources, scientists and doctors may cure these challenging diseases.

[vii]https://www.nejm.org/doi/full/10.1056/NEJMp1113569

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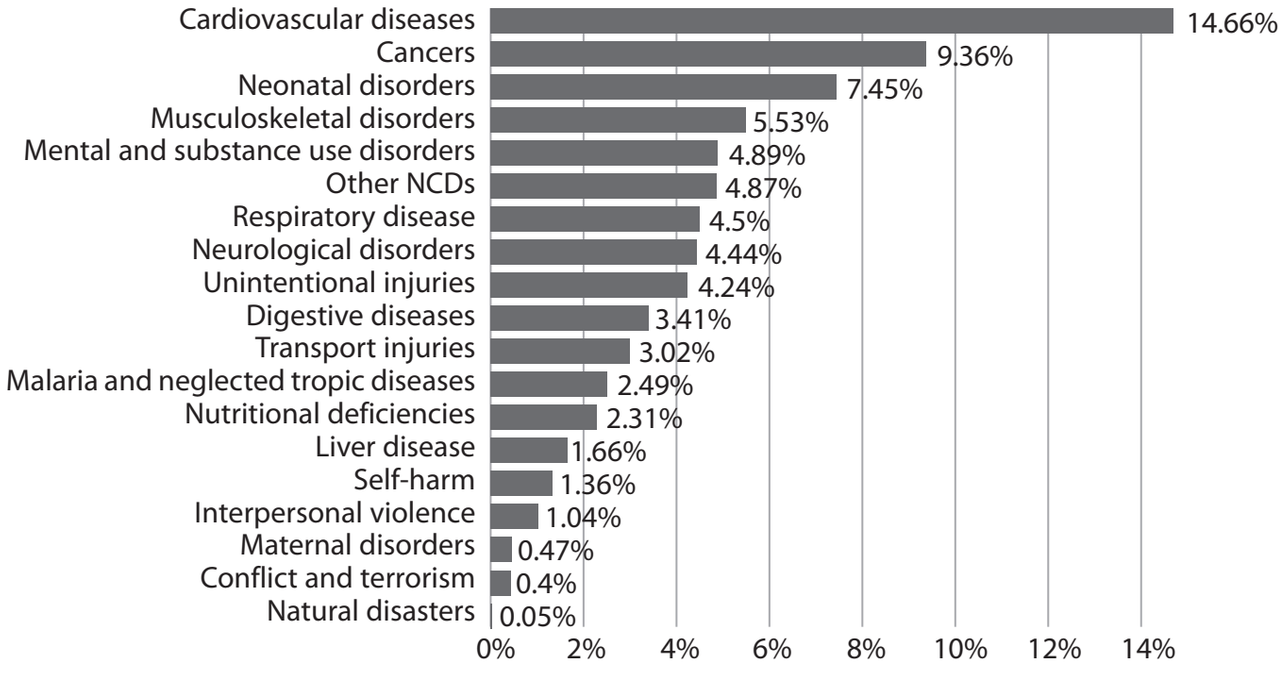
Share of total disease burden by cause, World, 2017

Total disease burden, measured in Disability-Adjusted Life Years (DALYs) by sub-category of disease or injury. DALYs measure the total burden of disease – both from years of life lost due to premature death and years lived with a disability. One DALY equals one lost year of healthy life.



(Source: IHME, Global Burden of Diseases
OurWorldInData.org/burden-of-disease • CC BY)

Figure 1

Today, six of the seven leading causes of death are non-communicable diseases (NCDs e.g. heart disease, stroke, lung diseases, cancer, Alzheimer's disease and diabetes). Based on the early promise mentioned above, regenerative medicine may be our best hope to solve the great non-communicable diseases of our time, and perhaps the single most transformative medical innovation in a century[viii].

[viii]https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

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Article 3

Current state of stem cell-based therapies: an overview

This is an edited version of an article published by the National Center for Biotechnology Information in May 2020. The article was written by Riham Mohamed Aly.

Introduction

Recent research reporting successful translation of stem cell therapies to patients has enriched the hope that such regenerative strategies may one day become a treatment for a wide range of hard-to-treat diseases. In fact, the past few years witnessed, an exponential increase in clinical trials revolving around stem cell-based therapies. Some of these trials resulted in remarkable impact on various diseases. In this review, the advances and challenges for the development of stem-cell-based therapies are described, with focus on the use of stem cells in dentistry in addition to the advances achieved in regenerative treatment modalities in several diseases. The limitations of these treatments and ongoing challenges in the field are also discussed while shedding light on the ethical and regulatory challenges in translating autologous stem cell-based interventions, into safe and effective therapies.

Cell-based therapy, an example of regenerative medicine, is considered one of the most promising disciplines in the areas of modern science and medicine. Such an advanced technology offers endless possibilities for potential cures for some of the most life-threatening diseases. Regenerative medicine is rapidly becoming the next big thing in health care with the particular aim of repairing and possibly replacing diseased cells, tissues or organs and eventually getting back to normal function. The prospect of regenerative medicine as an alternative to conventional drug-based therapies is becoming a reality owing to the vigorous commitment of the research communities in studying the potential applications across a wide range of diseases including neurodegenerative diseases and diabetes (1).

Recent research reporting successful stem cell therapies has enriched the hope that such regenerative strategies may one day become a treatment for a wide range of diseases (2). In fact, the past few years have seen an exponential advancement in clinical trials to do with stem cell-based therapies. Some of these trials resulted in remarkable impacts on various diseases (3). For example, a case of Epidermolysis Bullosa (EB) where the outer layer of skin does not properly adhere to the underlying layer, showed signs of skin recovery after treatment with cultures of skin stem cells (4). Also, a major improvement in eyesight of patients suffering from macular degeneration was reported after transplantation of patient-derived induced pluripotent stem cells (iPSCs) that were induced to differentiate into cells of the retina (5).

However, in spite of the increased amount of publications reporting successful cases of stem cell-based therapies, a major number of clinical trials have not yet acquired full regulatory approvals for validation as stem cell therapies. To date, the most established stem cell treatment is bone marrow transplants to treat blood and immune system disorders (1,6,7).

In this review, the advances and challenges for the development of stem-cell-based therapies are described, with focus on the use of stem cells in dentistry in addition to the advances reached in regenerative treatments in several diseases. The limitations of these treatments and ongoing challenges in the field are also discussed while considering the ethical and regulatory challenges in going from patient-derived stem cell-based interventions, into safe and effective therapies.

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Stem cell-based therapies

Stem cell-based therapies are defined as any treatment for a disease or a medical condition that involves the use of any type of human stem cell. Stem cells offer the perfect solution when there is a need for tissue and organ transplantation because they can differentiate into the specific cell types that are required for repair of diseased tissues.

However, the complexity of stem cell-based therapies often leads researchers to search for stable, safe and easily accessible stem cell sources that have the potential to differentiate into several cell types. Thus, it is of utmost importance to carefully select the type of stem cells that is most suitable for clinical application (7,9).

Stem cells hierarchy

There are mainly three types of stem cells. All three of them share the significant property of self-renewal (continued ability to divide) in addition to a unique ability to differentiate. However, it should be noted that stem cells are not all the same. Some have more potential than others so there is a hierarchy (10). The most undeveloped stem cells are the totipotent stem cells. These cells are capable of developing into a complete embryo and the extra-embryonic tissue e.g. the placenta. This unique property lasts for about 5 days; it starts with the fertilisation of the ovum and ends when the embryo reaches the four to eight cells stage. Following that stage, cells undergo more divisions until reaching the blastocyst (ball of cells) stage where they lose their totipotency property and develop a pluripotent identity where cells are only capable of differentiating into the three layers that will give rise to all the body tissues and organs. Cells of this stage are termed "embryonic stem cells (EPCs)" and are obtained by isolation from the inner cell mass of the blastocyst. This involves the destruction of the embryo. After consecutive divisions of these cells they are no longer pluripotent and their ability to differentiate becomes more restricted. The cells become multipotent (MSCs) meaning that they can only differentiate into limited types of cells related to the tissue of origin. This is the property of "adult stem cells", which are in all tissues, normally metabolically inactive, and help repair damaged tissues and replace dead cells throughout the lifetime of the organism. They include bone marrow and dental tissues among many others (11).

To many scientists adult stem cells are the best in stem cell-based therapies (12,13). Adult stem cells have demonstrated signs of clinical success especially in bone marrow transplants (14,15). In contrast to ESCs, adult stem cells are not subject to ethical or religious worries about where the cells come from. The fact that obtaining ESCs involves destruction of human embryos makes them unacceptable for a significant proportion of the population for ethical or religious reasons (16–18).

Turning point in stem cell research

In 2006 Shinya Yamanaka achieved a scientific breakthrough in stem cell research by generating cells that have the same properties and genetic profile of ESCs. He reprogrammed differentiated cells, obtained from connective tissue, into undifferentiated stem cells. He did this by adding four transcription factors. These transcription factors could switch back on genes that had been switched off during differentiation (19,20). These cells were called iPSCs (induced pluripotent stem cells) and Yamanaka's work has transformed the field of stem cell research (21). The most important feature of these cells is their ability to differentiate into any type of body cell, just like ESCs but without the ethical objections. Since they can be generated from the patient's own cells, iPSCs are a good possibility for the production of pluripotent patient-derived, matched cells that could be used for transplantation back into the patient. Nevertheless, a number of challenges still need to be investigated and addressed before iPSCs can be applied in cell therapies. Such challenges include; the detection and removal of incompletely differentiated cells and overcoming the tumorigenicity (potential to cause cancer) of these cells that could happen on transplantation (22).

Therapeutic translation of stem cell research

At the moment, some stem cell-based therapies using adult stem cells are clinically available and mainly include bone marrow transplants and skin grafts for severe burns (23). Up to the time of writing this article, there are more than 3,000 trials involving the use of adult stem cells registered in the World Health Organization (WHO) International Clinical Trials Registry.

In fact, the first clinical attempt using iPSCs reported successful results in treating the degenerative sight loss condition called macular degeneration (24). The outcomes of such trials will help the understanding of the timeframes needed to achieve successful therapies and also help gain a better understanding of the diseases. However, evaluation of stem cell-based therapies is not an easy task since transplantation of cells may result in tumour formation and other complications. This accounts for the variations in the results reported. The following section discusses the published data of some of the most important clinical trials involving the use of different types of stem cells both in medicine and in dentistry.

Stem cell-based therapy for neurodegenerative diseases

These include Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS) – a type of motor neurone disease, and multiple sclerosis (MS).

Parkinson's disease (PD)

PD is characterised by a rapid loss of brain neurones that produce the neurotransmitter dopamine. The first attempt to treat PD used human ESC cells. To avoid ethical controversies, the use of iPSCs was proposed (27).

In August 2018, Shinya Yamanaka initiated the first approved clinical trial to treat PD using iPSCs. Seven patients suffering from moderate PD were recruited (29). The trial involved the production of neurones able to produce dopamine and then the surgical transplantation of these neurones into the brains of the patients. In addition, immunosuppressant drugs were given to avoid rejection. Preliminary results so far showed the treatment to be safe.

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Multiple sclerosis (MS)

MS is an inflammatory and neurodegenerative autoimmune (the patient's immune system attacks their own tissues) disease of the central nervous system. Stem cell-based therapies are now exploring the possibility of halting the disease progression and of reversing the damage to nerves. A registered phase 1 clinical trial was carried out by the company Celgene™ in 2014 using adult stem cells to treat patients suffering from MS (30). This trial was performed at 6 centres in the United States and 2 centres in Canada and included 16 patients. Results demonstrated that the treatment was safe. However, clinical responses from patients indicated that the treatment did not improve the MS condition (31). A therapy that involves removing the patient's immune system and replacing it with a bone marrow transplant has led to remission (relief from the symptoms) (32). However, some patients suffered complications such as infertility and neurological disabilities. A number of randomised controlled trials are planned to answer these concerns (32). Currently, new and innovative stem cell-based therapies for MS are only in the initial stages, and are based on the possibility of replacing damaged nerve tissue with nerve cells derived from iPSCs. However, the potential of using iPSCs in treatments is still the subject of research (33).

Spinal cord injury

Stem cells have the potential to treat spinal cord injuries. The transplantation of different forms of nerve stem cells has led to growth in the axons of neurones as well as to an increase in connections between neurones (36). However, proof of recovered function has yet to be shown in clinical trials. Nevertheless, Japan has recently given approval to stem-cell treatment for spinal-cord injuries. This approval was based on clinical trials that are yet to be published and involve 13 patients, who are suffering from recent spinal-cord injury. The Japanese team discovered that injection of stem cells isolated from the patients' bone marrow led to them gaining some sensation and mobility.

This is the first stem cell-based therapy targeting spinal-cord injuries to gain government approval to offer to patients (37).

Stem cell-based therapies for ocular (eye) diseases

A huge number of the currently registered clinical trials for stem cell-based therapies target eye diseases. This is mainly due to the fact that many parts of the eye are out of reach of the immune system. Most of these trials are happening in various countries including Japan, China, Israel, Korea, UK, and USA and they use ESCs from donors (35,36).

Notably, the first clinical trial to introduce the use of patient-derived iPSCs to make retinal cells for transplantation was in Japan. It followed the new regulatory laws issued in 2014 by Japan's government to regulate regenerative medicine applications. Two patients were recruited in this trial; the first one received treatment for macular degeneration using retinal cells generated from iPSCs (37). After 1 year of follow-up, there were no signs of serious complications or tumours. Moreover, there were no signs of rejection of the transplanted cells in the second year follow-up. Most importantly, the patients reported improvement in their vision. These results were enough to conclude that iPSCs-based transplantation was safe and possible (38).

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Stem cell-based therapies for treatment of diabetes

Pancreatic beta cells are destroyed in type 1 diabetes mellitus, because of disorders in the immune system. It is an autoimmune disease. Type 2 diabetes is caused by failure of the beta-cells to produce enough insulin and a failure of insulin receptors on cells to detect and respond to the insulin. Several genes are involved and also many environmental factors and type 2 diabetes can be prevented or reversed with changes in lifestyle.

In both cases the affected cells are the beta cells in the islets of Langerhans and, since the pancreas does not efficiently regenerate islets from endogenous adult stem cells, other cell sources were tested (38). Pluripotent stem cells (PSCs) are considered the cells of choice for beta cell replacement strategies (39). At the moment, there are a few clinical trials targeting beta cell replacement using ESCs. These trials involve the insertion of insulin-producing beta cells, in a capsule, under the skin (40). The company ViaCyte™ in California initiated a trial* in 2014 in collaboration with Harvard University.
*https://clinicaltrials.gov/ct2/show/NCT02239354

This involved 40 patients and used two capsules of insulin-producing beta cells generated from ESCs. This demonstrated successful blood glucose level regulation. The capsules were taken out after 174 days and found to contain insulin-producing cells (41).

Stem cells in dentistry

MSCs have been isolated from dental tissues such as dental pulp (the central part) of adult and infant teeth and surrounding tissues (42–44). These cells were described as an excellent cell source owing to their ease of accessibility, their ability to differentiate into bone-forming cells and tooth-forming cells and for their lack of ethical controversies (45). However, assessments of stem cells after transplantation still require extensive studying. The results of clinical trials have yet to be fully evaluated. However, stem cell-based dental regeneration may soon be a readily available treatment.

Dental pulp regeneration

The first human clinical study using patient-derived dental pulp stem cells (DPSCs) for complete pulp regeneration was reported by Nakashima et al. in 2017 (49). Patients with irreversible pulpitis (inflammation of the pulp cavity) were recruited and followed up for 6 months following DPSCs transplantation. The research team reported that the use of DPSCs seeded on collagen (a protein found in many body tissues) – the connective tissue scaffold in molars and premolars, was safe. No harmful events or toxicity were demonstrated. Magnetic resonance imaging (MRI scans) of the new tissues formed in the root canal showed successful pulp regeneration. A different group conducted a clinical trial where patient-derived stem cells from their infant teeth were employed to induce pulp regeneration (51). Follow-up of the cases a year after the intervention reported evidence of pulp regeneration with new blood and nerve supplies. In addition, no signs of adverse effects were observed. Both trials are proceeding with the next phases. The results obtained are promising.

Regeneration of mandibular (jaw) bony defects

The first clinical study using DPSCs for facial bone regeneration was conducted in 2009 (53). Patients in this study suffered from extreme bone loss following extraction of wisdom teeth. Three years later, the same group published a report evaluating the stability and quality of the regenerated bone after DPSCs transplantation (54). The newly formed bone was uniformly vascularised (supplied with blood vessels). However, it was of compact bone rather than spongy bone, which is usually the type of bone in this region.

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Stem cells and tissue banks

The ability to bank stem cells at their most potent state for later use is essential for stem cell-based therapies. In order to be considered valid, any new stem cell-based therapy should be as effective as the routine treatment. When evaluating a type of stem cell for use in cellular therapies, issues such as immune rejection must be avoided and, at the same time, large numbers of stem cells must be readily available before clinical use. iPSCs theoretically possess the ability for unlimited division which makes them an attractive source for use in cell-based therapies. Unlike adult stem cells, the ability of iPSCs to continue to divide does not decrease with time (22). Recently, California Institute for Regenerative Medicine (CIRM) has introduced an iPSCs bank to provide researchers with iPSCs cell lines in order to accelerate stem cell treatments through studying genetic variation and disease modelling.

Another important source for stem cells banking is the umbilical cord. Umbilical cord is immediately preserved at low temperature after birth, which permits stem cells to be successfully stored and be ready for use in cell-based therapies for incurable diseases. However, stem cells from human infant teeth are more attractive as a source for stem cell banking. These cells have the capacity to differentiate into more cell types than the rest of the adult stem cells can (56). Moreover, procedures involving the isolation and freezing of these cells are uncomplicated. The most important advantage of banking infant teeth for specific individuals is for transplants that avoid the possibility of rejection (57). Unlike cord blood stem cells, teeth stem cells have the ability to differentiate into connective tissues, neural and dental tissues (58). Finally, the ultimate goal of stem cell banking, is to establish a repository of high-quality stem cell lines derived from many individuals for future use in therapy.

Current regulatory guidelines for stem cell-based therapies

With the increased number of clinical trials employing stem cells, the need for developing regulatory guidelines and standards to ensure patient safety is becoming more and more essential. However, the fact that stem cell therapy is rather a new area makes it subject to scientific, ethical and legal controversies that are yet to be regulated. Leading countries in the field have devised guidelines for that purpose. In the USA, the Food and Drug Administration (FDA) has released regulatory guidelines to ensure that these treatments are safe and effective (59). In 2014, a radical regulatory reform in Japan occurred with the passing of two new laws that permitted conditional approval of cell-based treatments following early phase clinical trials on the condition that clinical safety data are provided from at least ten patients. These laws allow skipping most of the traditional criteria of clinical trials in what was described as "fast track approvals" and treatments were classified according to risk (60). To date, the treatments that acquired conditional approval include those targeting spinal-cord injury and cardiac disease (61).

Challenges and ethical issues facing stem cell-based therapies

Stem cell-based therapies face many obstacles that need to be urgently addressed. The most persistent concern is the ethical conflict regarding the use of ESCs. As previously mentioned, ESCs are far superior regarding their potency; however, obtaining them requires destruction of human embryos, obtained from spare embryos created during IVF treatments. True, the discovery of iPSCs overcame this concern. Nevertheless, iPSCs themselves currently face another ethical controversy which addresses their unlimited capacity of differentiation with concerns that these cells could one day be used for human cloning. The use of iPSCs in therapy is still considered a high-risk treatment, since transplantation of these cells could induce tumour (cancer) formation. Such challenge is currently addressed through developing protocols to ensure their safety in addition to developing global clinical-grade iPSCs cell lines before these cells are available for clinical use (61). As for MSCs, these cells have been universally considered safe. However, continuous monitoring and prolonged follow-up should be the focus of future research to avoid the possibility of tumour formation after treatments (62).

Finally, it could be proposed that one of the most challenging ethical issues, faced in the field of stem cell-based therapies at the moment, is the increasing number of clinics offering unproven stem cell-based treatments. Researchers are thus morally obliged to ensure that ethical considerations are not undermined in trying to make progress in clinical use.

Conclusions

Stem cell therapy is becoming a reality by the day, thanks to the increasing amount of research conducted over the past decade. With every research conducted the possibilities of stem cell applications increased in spite of the many challenges faced. Currently, progress in the area of stem cells is very promising with reports of clinical success in treating various diseases such as neurodegenerative diseases and macular degeneration, progressing rapidly. iPSCs are conquering the field of stem cell research with endless possibilities of treating diseases using patients' own cells. Regeneration of dental tissues has made its way to the clinic and soon enough will become a valid treatment. Although challenges might seem daunting, stem cell research is advancing rapidly and cellular therapies will soon be used. Fortunately, there are currently tremendous efforts exerted globally towards setting up regulatory guidelines and standards to ensure patient safety. In the near future, stem cell-based therapies shall significantly improve human health.

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References

This article has been edited and some references have been removed from the list.

1. Chari S, Nguyen A, Saxe J. Stem Cells in the Clinic. *Cell Stem Cell* 2018;22:781–2. 10.1016/j.stem.2018.05.017 [PubMed] [CrossRef] [Google Scholar]

2. Madl CM, Heilshorn SC, Blau HM. Bioengineering strategies to accelerate stem cell therapeutics. *Nature* 2018;557:335–42. 10.1038/s41586-018-0089-z [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Pérez López S, Otero Hernández J. Advances in stem cell therapy. *Adv Exp Med Biol* 2012;741:290–313. 10.1007/978-1-4614-2098-9_19 [PubMed] [CrossRef] [Google Scholar]

4. Hirsch T, Rothoeft T, Teig N, et al. Regeneration of the entire human epidermis using transgenic stem cells. *Nature* 2017;551:327-32. 10.1038/nature24487 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Mandai M, Kurimoto Y, Takahashi M. The authors reply. Vol. 377, *New England Journal of Medicine*. Massachusetts Medical Society, 2017:792–3. [Google Scholar]

6. Trounson A, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. *Cell Stem Cell* 2015;17:11–22. 10.1016/j.stem.2015.06.007 [PubMed] [CrossRef] [Google Scholar]

7. De Luca M, Aiuti A, Cossu G, et al. Advances in stem cell research and therapeutic development. *Nat Cell Biol* 2019;21:801–11. 10.1038/s41556-019-0344-z [PubMed] [CrossRef] [Google Scholar]

9. Bobba S, Di Girolamo N, Munsie M, et al. The current state of stem cell therapy for ocular disease. *Exp Eye Res* 2018;177:65–75. 10.1016/j.exer.2018.07.019 [PubMed] [CrossRef] [Google Scholar]

10. Gaskell T, Englund MCO, Hyllner J. Human embryonic stem cells. In: Steinhoff G. editor. Regenerative Medicine – from Protocol to Patient: 2. Stem Cell Science and Technology. 3rd edition. Springer, 2016. [Google Scholar]

11. Clevers H, Watt FM. Defining Adult Stem Cells by Function, not by Phenotype. *Annu Rev Biochem* 2018;87:1015–27. 10.1146/annurev-biochem-062917-012341 [PubMed] [CrossRef] [Google Scholar]

12. Prentice DA. Adult Stem Cells. *Circ Res* 2019;124:837–9. 10.1161/CIRCRESAHA.118.313664 [PubMed] [CrossRef] [Google Scholar]

13. Lukomska B, Stanaszek L, Zuba-Surma E, et al. Challenges and Controversies in Human Mesenchymal Stem Cell Therapy. *Stem Cells Int* 2019;2019:9628536. [PMC free article] [PubMed]

14. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. *Nature* 2014;505:327–34. 10.1038/nature12984 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

15. Sharpe M, Leoni G, Hyllner J. Stem Cells. In: McQueen CA. Comprehensive Toxicology. 3rd edition. Elsevier, 2017:23–59. [Google Scholar]

16. Green RM. Ethical Considerations. In: Lanza R, Atala A. editors. Essentials of Stem Cell Biology. 3rd edition. Elsevier, 2013:595–604. [Google Scholar]

17. Brignier AC, Gewirtz AM. Embryonic and adult stem cell therapy. *J Allergy Clin Immunol* 2010;125:S336–44. 10.1016/j.jaci.2009.09.032 [PubMed] [CrossRef] [Google Scholar]

18. Lo B, Parham L. Ethical issues in stem cell research. *Endocr Rev* 2009;30:204–13. 10.1210/er.2008-0031 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

19. Takahashi K, Yamanaka S. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell* 2006;126:663–76. 10.1016/j.cell.2006.07.024 [PubMed] [CrossRef] [Google Scholar]

20. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell* 2007;131:861–72. 10.1016/j.cell.2007.11.019 [PubMed] [CrossRef] [Google Scholar]

21. Shi Y, Inoue H, Wu JC, et al. Induced pluripotent stem cell technology: a decade of progress. *Nat Rev Drug Discov* 2017;16:115–30. 10.1038/nrd.2016.245 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

22. Attwood SW, Edel MJ. iPS-Cell Technology and the Problem of Genetic Instability–Can It Ever Be Safe for Clinical Use? *J Clin Med* 2019;8:288. 10.3390/jcm8030288 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

23. Poulos J. The limited application of stem cells in medicine: a review. *Stem Cell Res Ther* 2018;9:1. 10.1186/s13287-017-0735-7 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

24. Mandai M, Watanabe A, Kurimoto Y, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. *N Engl J Med* 2017;376:1038–46. 10.1056/NEJMoa1608368 [PubMed] [CrossRef] [Google Scholar]

27. Kikuchi T, Morizane A, Doi D, et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. *Nature* 2017;548:592–6. 10.1038/nature23664 [PubMed] [CrossRef] [Google Scholar]

29. Takahashi J. Stem cell therapy for Parkinson's disease. *Expert Rev Neurother* 2007;7:667–75. 10.1586/14737175.7.6.667 [PubMed] [CrossRef] [Google Scholar]

30. Lublin FD, Bowen JD, Huddlestone J, et al. Human placenta-derived cells(pda-001) for the treatment of adults with multiple sclerosis: A randomized, placebo-controlled, multiple-dose study. *Mult Scler Relat Disord* 2014;3:696–704. 10.1016/j.msard.2014.08.002 [PubMed] [CrossRef] [Google Scholar]

31. Cuascut FX, Hutton GJ. Stem Cell-Based Therapies for Multiple Sclerosis: Current Perspectives. *Biomedicines* 2019;7:26. 10.3390/biomedicines7020026 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

32. Delemarre EM, Van Den Broek T, Mijnheer G, et al. Autologous stem cell transplantation AIDS autoimmune patients by functional renewal and TCR diversification of regulatory T cells. *Blood* 2016;127:91–101. 10.1182/blood-2015-06-649145 [PubMed] [CrossRef] [Google Scholar]

33. Thiruvalluvan A, Czepiel M, Kap YA, et al. Survival and Functionality of Human Induced Pluripotent Stem Cell-Derived Oligodendrocytes in a Non-human Primate Model for Multiple Sclerosis. *Stem Cells Transl Med* 2016;5:1550–61. 10.5966/sctm.2016-0024 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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35. Mazzini L, Ferrari D, Andjus PR, et al. Advances in stem cell therapy for amyotrophic lateral sclerosis. *Expert Opin Biol Ther* 2018;18:865–81. 10.1080/14712598.2018.1503248 [PubMed] [CrossRef] [Google Scholar]

36. Assinck P, Duncan GJ, Hilton BJ, et al. Cell transplantation therapy for spinal cord injury. *Nat Neurosci* 2017;20:637–47. 10.1038/nn.4541 [PubMed] [CrossRef] [Google Scholar]

37. Cyranoski D. Japan's approval of stem-cell treatment for spinal-cord injury concerns scientists. *Nature* 2019;565:544–5. 10.1038/d41586-019-00178-x [PubMed] [CrossRef] [Google Scholar]

38. Dor Y, Brown J, Martinez OI, et al. Adult pancreatic β-cells are formed by self-duplication rather than stem-cell differentiation. *Nature* 2004;429:41–6. 10.1038/nature02520 [PubMed] [CrossRef] [Google Scholar]

39. Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells *in vitro. Cell* 2014;159:428–39. 10.1016/j.cell.2014.09.040 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

40. Schulz TC, Young HY, Agulnick AD, et al. A scalable system for production of functional pancreatic progenitors from human embryonic stem cells. *PLoS One* 2012;7:e37004. 10.1371/journal.pone.0037004 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

41. Vegas AJ, Veiseh O, Gürtler M, et al. Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice. Nat Med 2016;22:306–11. 10.1038/nm.4030 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

42. Raspini G, Wolff J, Helminen M, et al. Dental Stem Cells Harvested from Third Molars Combined with Bioactive Glass Can Induce Signs of Bone Formation *In Vitro*. *J Oral Maxillofac Res* 2018;9:e2. 10.5037/jomr.2018.9102 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

43. Yasui T, Mabuchi Y, Morikawa S, et al. Isolation of dental pulp stem cells with high osteogenic potential. *Inflamm Regen* 2017;37:8. 10.1186/s41232-017-0039-4 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

44. Suchánek J, Visek B, Soukup T, et al. Stem cells from human exfoliated deciduous teeth-isolation, long term cultivation and phenotypical analysis. *Acta Medica* (*Hradec Kralove*) 2010;53:93–9. 10.14712/18059694.2016.66 [PubMed] [CrossRef] [Google Scholar]

45. Hu L, Liu Y, Wang S. Stem cell-based tooth and periodontal regeneration. *Oral Dis* 2018;24:696–705. 10.1111/odi.12703 [PubMed] [CrossRef] [Google Scholar]

49. Nakashima M, Iohara K, Murakami M, et al. Pulp regeneration by transplantation of dental pulp stem cells in pulpitis: a pilot clinical study. *Stem Cell Res Ther* 2017;8:61. 10.1186/s13287-017-0506-5 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

51. Xuan K, Li B, Guo H, et al. Deciduous autologous tooth stem cells regenerate dental pulp after implantation into injured teeth. *Sci Transl Med* 2018;10:eaaf3227. [PubMed]

53. d'Aquino R, De Rosa A, Lanza V, et al. Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes. *Eur Cell Mater* 2009;18:75–83. 10.22203/eCM.v018a07 [PubMed] [CrossRef] [Google Scholar]

54. Giuliani A, Manescu A, Langer M, et al. Three Years After Transplants in Human Mandibles, Histological and In-Line Holotomography Revealed That Stem Cells Regenerated a Compact Rather Than a Spongy Bone: Biological and Clinical Implications. *Stem Cells Transl Med* 2013;2:316–24. 10.5966/sctm.2012-0136 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

56. Ma L, Makino Y, Yamaza H, et al. Cryopreserved Dental Pulp Tissues of Exfoliated Deciduous Teeth Is a Feasible Stem Cell Resource for Regenerative Medicine. *PLoS One* 2012;7:e51777. 10.1371/journal.pone.0051777 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

57. Arora V, Arora P, Munshi AK. Banking stem cells from human exfoliated deciduous teeth (SHED): saving for the future. *J Clin Pediatr Dent* 2009;33:289–94. 10.17796/jcpd.33.4.y887672r0j703654 [PubMed] [CrossRef] [Google Scholar]

58. Cordeiro MM, Dong Z, Kaneko T, et al. Dental Pulp Tissue Engineering with Stem Cells from Exfoliated Deciduous Teeth. *J Endod* 2008;34:962–9. 10.1016/j.joen.2008.04.009 [PubMed] [CrossRef] [Google Scholar]

59. Marks PW, Witten CM, Califf RM. Clarifying Stem-Cell Therapy's Benefits and Risks. *N Engl J Med* 2017;376:1007–9. 10.1056/NEJMp1613723 [PubMed] [CrossRef] [Google Scholar]

60. Konomi K, Tobita M, Kimura K, et al. New Japanese initiatives on stem cell therapies. *Cell Stem Cell* 2015;16:350–2. 10.1016/j.stem.2015.03.012 [PubMed] [CrossRef] [Google Scholar]

61. Cyranoski D. The potent effects of Japan's stem-cell policies. *Nature* 2019;573:482–5. 10.1038/d41586-019-02847-3 [PubMed] [CrossRef] [Google Scholar]

62. Volarevic V, Markovic BS, Gazdic M, et al. Ethical and safety issues of stem cell-based therapy. *Int J Med Sci* 2018;15:36–45. 10.7150/ijms.21666 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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